

**NATIONAL GUIDELINE CLEARINGHOUSE™ (NGC™)
GUIDELINE SYNTHESIS**

**CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)
PART I. DIAGNOSIS AND MANAGEMENT OF STABLE COPD**

Guidelines

1. Veterans Health Administration/Department of Veterans Affairs (VHA/DOD). [Clinical practice guideline for the management of persons with chronic obstructive pulmonary disease](#). Washington (DC): Department of Veterans Affairs; 1999. 116 p. [193 references].
2. World Health Organization/National Heart, Lung, and Blood Institute (WHO/NHLBI). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Global Initiative for Chronic Obstructive Lung Disease, 2001. Various p. [547 references].
CURRENT NGC SUMMARY: [Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease](#).

***Please note:** The GOLD guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this synthesis.

INTRODUCTION:

A direct comparison of Veterans Health Administration/Department of Veterans Affairs (VHA/DOD) and World Health Organization/National Heart, Lung, and Blood Institute (WHO/NHLBI) recommendations for the diagnosis and management of chronic obstructive pulmonary disease (COPD) is provided in the tables below. The VHA/DOD and WHO/NHLBI guidelines are very broad in scope, providing recommendations on diagnosis and management of both stable COPD and acute exacerbations of disease. The WHO/NHLBI guideline also addresses prevention strategies. Diagnosis and management of acute exacerbations of COPD are compared in [Part II](#) of this synthesis. Recommendations for pulmonary rehabilitation of patients with COPD are addressed in Part III of this synthesis.

Following the [content comparison table](#) and discussion, the areas of agreement and differences among the guidelines are identified. The evidence surrounding disparate recommendations is explored in the discussion of areas of difference.

Abbreviations:

- AAT, Alpha1-antitrypsin
- COPD, Chronic obstructive pulmonary disease
- FEV₁, Forced expiratory volume in one second
- FVC, Forced vital capacity

- LTOT, Long-term oxygen therapy
- SAIBA, Short-acting inhaled beta₂ agonist
- VHA/DOD, Veterans Health Administration/Department of Veterans Affairs
- VC, Vital capacity
- WHO/NHLBI, World Health Organization/National Heart, Lung, and Blood Institute

Note: To print the following tables, users may have to change their printer settings to landscape, print on legal size paper, and/or use a small font size.

TABLE 1: COMPARISON OF SCOPE AND CONTENT		
	VHA/DOD (1999)	WHO/NHLBI (2001)
OBJECTIVE AND SCOPE	<ul style="list-style-type: none"> • To assist primary care providers or specialists in the early detection of symptoms, assessment of the clinical situation, determination of appropriate treatment, and delivery of individualized interventions. • To provide enough guidance for a broad range of clinical settings, while at the same time providing enough flexibility to accommodate local practice and individual situations. • To promote evidence-based management of persons with chronic obstructive pulmonary disease (COPD) and thereby improve clinical outcomes. 	<ul style="list-style-type: none"> • To recommend effective COPD management and prevention strategies for use in all countries. • To increase awareness of the medical community, public health officials and the general public that COPD is a public health problem. • To decrease morbidity and mortality from COPD through implementation and evaluation of effective programs for diagnosis and management. • To promote study into reasons for increasing prevalence of COPD including relationship with environment. • To implement effective programs to prevent COPD.
TARGET POPULATION	<p>Veterans with COPD</p> <p><i>Note: This guideline includes recommendations for patients with both chronic stable disease and</i></p>	<p>Individuals with COPD</p> <p><i>Note: This guideline includes recommendations for patients with both chronic stable disease and patients with acute</i></p>

	<p>patients with acute exacerbations of COPD. For recommendations concerning acute exacerbation of COPD, see Part II of this synthesis.</p>	<p>exacerbations of COPD. For recommendations concerning acute exacerbation of COPD, see Part II of this synthesis.</p>
INTENDED USERS	Physicians; Nurses; Nurse Practitioners; Physician Assistants; Respiratory Care Practitioners	Physicians; Physician Assistants; Respiratory Care Practitioners; Nurse Practitioners; Nurses; Allied Health Care Practitioners; Public Health Departments
INTERVENTIONS AND PRACTICES CONSIDERED	<p><i>Outpatient management of chronic obstructive pulmonary disease (COPD)</i></p> <ol style="list-style-type: none"> Clinical assessment: <ul style="list-style-type: none"> Assessment of symptoms Medical history Physical exam: including assessment of airflow obstruction Laboratory tests: including spirometry, chest x-ray, blood gas analysis, alpha1-antitrypsin level Evaluate for acute and/or severe exacerbation Pre- and postbronchodilation spirometry Pharmacotherapy <ul style="list-style-type: none"> Inhaled anticholinergic therapy (ipratropium) Long-acting inhaled beta₂-agonists 	<p><i>Assessment/Diagnosis</i></p> <ol style="list-style-type: none"> Initial diagnosis <ul style="list-style-type: none"> Assessment of symptoms Medical history Physical examination Measurement of airflow limitation (spirometry) Assessment of severity Additional investigations, including chest x-ray, electrocardiography, blood gas analysis, alpha1-antitrypsin levels Differential diagnosis Ongoing monitoring and assessment <ul style="list-style-type: none"> Monitor disease progression and development of complications Monitor pharmacotherapy and other medical treatment Monitor exacerbation history Monitor comorbidities <p><i>Risk Factor Reduction</i></p>

	<p>(LAIBA) (salmeterol)</p> <ul style="list-style-type: none"> • Short-acting inhaled beta₂-agonists (SAIBA) (albuterol, metaproterenol, terbutaline) • Combination therapy with inhaled anticholinergics and short acting beta₂-agonists • Inhaled medication using metered dose inhaler (MDI) or nebulizer (NEB) • Systemic corticosteroid therapy (prednisone) • Theophylline trial • Theophylline combination therapy <p>5. Long-term oxygen therapy</p> <p>6. Preoperative evaluation and management</p> <p>7. Air travel management, including oxygen supplementation</p> <p>8. Insomnia management</p> <p>9. Patient education and preventive care</p> <ul style="list-style-type: none"> • Immunizations • Smoking cessation • Management of environment <p>10. Follow-up and continuing</p>	<p>1. Smoking prevention and cessation</p> <p>2. Occupational exposures</p> <p>3. Indoor/outdoor air pollution</p> <p><i>Management of stable COPD</i></p> <p>1. Education</p> <p>2. Pharmacologic treatment</p> <ul style="list-style-type: none"> • Bronchodilators (beta₂-agonists, anticholinergics) • Glucocorticosteroids • Other pharmacologic treatments <p>3. Non-pharmacologic treatment</p> <ul style="list-style-type: none"> • Pulmonary rehabilitation • Oxygen therapy • Ventilatory support • Surgical treatments <p><i>Management of exacerbations</i></p> <p>1. Home management</p> <p>2. Hospital management</p> <p><i>Note: For specific interventions concerning diagnosis and management of acute exacerbations of COPD, see Part II of this synthesis. For interventions on pulmonary rehabilitation, see Part III of this synthesis.</i></p>
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	<p>assessment</p> <p><i>Inpatient Management of Chronic Obstructive Pulmonary Disease</i></p> <p><i>Note: For specific interventions concerning diagnosis and management of acute exacerbations of COPD, see Part II of this synthesis.</i></p>	
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TABLE 2: COMPARISON OF RECOMMENDATIONS FOR DIAGNOSIS AND MANAGEMENT OF STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) <i>Diagnosis and Initial Assessment</i>		
	VHA/DOD (1999)	WHO/NHLBI (2001)
Definition of COPD	COPD is a disorder characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema; the airflow obstruction is generally slowly progressive, may be accompanied by airway hyperactivity, and may be partially reversible.	COPD is a disease characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. A diagnosis of COPD should be considered in any patient who has symptoms of cough, sputum production, or dyspnea, and/or a history of exposure to risk factors for the disease.
Medical history	<p>Medical history should include evaluations of the following:</p> <ol style="list-style-type: none"> Smoking: Age at initiation, quantity smoked per day, whether or not still smoker and if not, date of cessation. 	<p>A detailed medical history of a new patient known or thought to have COPD should assess:</p> <ul style="list-style-type: none"> Exposure to risk factors. Past medical history, including asthma, allergy, sinusitis or nasal polyps, respiratory

	<ul style="list-style-type: none"> b. Environmental (chronological), e.g., dust exposure (may disclose important risk factors). c. Cough (chronic, productive): Frequency and duration, whether or not productive (especially on awakening). d. Wheezing. e. Acute chest illnesses: Frequency, productive cough, wheezing, dyspnea, fever. f. Dyspnea. g. Evaluate current therapy. <p>Other critical elements of history:</p> <ul style="list-style-type: none"> a. Baseline respiratory status b. Exercise limitations c. Sleep and eating difficulties d. Home care resources e. Home therapeutic regimen f. Symptoms of co-morbid acute and chronic conditions 	<p>infections in childhood, and other respiratory diseases.</p> <ul style="list-style-type: none"> • Family history of COPD or other chronic respiratory disease. • Pattern of symptom development. • History of exacerbations or previous hospitalizations for respiratory disorder. • Presence of comorbidities, such as heart disease and rheumatic disease, that may also contribute to restriction of activity. • Appropriateness of current medical treatments. • Impact of disease on patients life, including limitation of activity; missed work and economic impact; effect on family routines; and feelings of depression or anxiety. • Social and family support available to the patient. • Possibilities for reducing risk factors, especially smoking cessation.
Physical examination	<p>Critical elements of the clinical assessment include:</p> <ul style="list-style-type: none"> a. Temperature b. Respiratory rate c. Heart rate d. Cyanosis e. Accessory muscle use f. Edema g. Cor pulmonale h. Bronchospasm i. Hemodynamic instability j. Paradoxical abdominal retractions k. Pneumonia 	<p>Though an important part of patient care, a physical examination is rarely diagnostic in COPD. Physical signs of airflow limitation are rarely present until significant impairment of lung function has occurred, and their detection has a relatively low sensitivity and specificity.</p> <p><i>Inspection:</i></p> <ul style="list-style-type: none"> • Central cyanosis, or bluish discoloration of the mucosal

	<p>I. Altered mentation</p> <p>Physical examination of chest should include the following evaluations:</p> <ol style="list-style-type: none"> Airflow obstruction evidenced by: <ul style="list-style-type: none"> Wheezing during auscultation on slow or forced breathing. Forced expiratory time of more than 6 seconds. Severe emphysema indicated by: <ul style="list-style-type: none"> Overdistention of lungs in stable state, low diaphragmatic position. Decreased intensity of breath and heart sounds. Severe disease suggested by (characteristics not diagnostic): <ul style="list-style-type: none"> Pursed-lip breathing. Use of accessory respiratory muscles. Indrawing of lower interspaces. Other: Unusual positions to relieve dyspnea at rest, digital clubbing (suggests possibility of lung cancer or bronchiectasis), and mild dependent edema that may be seen in absence of right heart failure. 	<p>membranes, may be present but is difficult to detect in artificial light and in many racial groups.</p> <ul style="list-style-type: none"> Common chest wall abnormalities, which reflect the pulmonary hyperinflation seen in COPD, include relatively horizontal ribs, "barrel-shaped" chest, and protruding abdomen. Flattening of the hemidiaphragms may be associated with paradoxical in-drawing of the lower rib cage on inspiration, reduced cardiac dullness, and widening xiphisternal angle. Resting respiratory rate is often increased to more than 20 breaths per minute and breathing can be relatively shallow. Patients commonly show pursed-lip breathing, which may serve to slow expiratory flow and permit more efficient lung emptying. COPD patients often have resting muscle activation while lying supine. Use of the scalene and sternocleidomastoid muscles is a further indicator of respiratory distress. Ankle or lower leg edema can be a sign of right heart failure. <p><i>Palpation and percussion</i></p> <ul style="list-style-type: none"> These are often unhelpful in COPD. Detection of the heart apex beat may be difficult due to
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		<p>pulmonary hyperinflation.</p> <ul style="list-style-type: none"> • Hyperinflation also leads to downward displacement of the liver and an increase in the ability to palpate this organ without it being enlarged. <p><i>Auscultation</i></p> <ul style="list-style-type: none"> • Patients with COPD often have reduced breath sounds, but this finding is not sufficiently characteristic to make the diagnosis. • The presence of wheezing during quiet breathing is a useful pointer to airflow limitation. However, wheezing heard only after forced expiration is of no diagnostic value. • Inspiratory crackles occur in some COPD patients but are of little help diagnostically. • Heart sounds are best heard over the xiphoid area.
<p>Measurement of airflow limitation — Spirometry</p>	<p>On initial visit: Spirometry pre- and postbronchodilation are essential to confirm presence and reversibility of airflow obstruction and to quantify maximum level of ventilatory function, guide management, and estimate prognosis.</p> <p>On follow up visits: Repeat spirometry if major change in patients condition. On new patients previous spirometry may be used if available and no change in patient's condition.</p>	<p>To help identify patients earlier in the course of the disease, spirometry should be performed for patients who have chronic cough and sputum production and a history of exposure to risk factors, even if they do not have dyspnea. Spirometry should measure the maximal volume of air forcibly exhaled from the point of maximal inhalation (forced vital capacity, FVC) and the volume of air exhaled during the first second of this maneuver (forced expiratory volume in one second,</p>

	<ol style="list-style-type: none"> 1. Airflow limitation is diagnosed by a reduction in FEV_1/VC. 2. Lung volumes: Unnecessary except in special circumstances (e.g., coexisting interstitial lung disease, presence of giant bullae, and decrease in VC). 3. Carbon monoxide diffusing capacity: Unnecessary except in special instances (e.g., dyspnea out of proportion to severity of airflow limitation). 	<p>FEV_1), and the ratio of these two measurements (FEV_1/FVC) should be calculated. Patients with COPD typically show a decrease in both FEV_1 and FVC. The presence of a postbronchodilator $FEV_1 < 80\%$ of the predicted value in combination with an $FEV_1/FVC < 70\%$ confirms the presence of airflow limitation that is not fully reversible. The FEV_1/FVC on its own is a more sensitive measure of airflow limitation, and an $FEV_1/FVC < 70\%$ is considered an early sign of airflow limitation in patients whose FEV_1 remains normal ($\geq 80\%$ predicted). This approach to defining airflow limitation is a pragmatic one in view of the fact that universally applicable reference values for FEV_1 and FVC are not available.</p>
Assessing severity of disease	<p>COPD severity can be graded on the basis of percentage of predicted FEV_1 as <i>mild</i>, <i>moderate</i>, or <i>severe</i>. Grading or staging, based on severity of airflow obstruction, facilitates the application of clinical recommendations and attempts to offer a composite picture of disease severity. Forced expiratory spirometry is used in the diagnosis of COPD as well as in the assessment of its severity, progression, and prognosis. The use of an $FEV_1 \leq 50$ percent corresponds to a grade of moderate to severe as adopted in the 1995 American Thoracic Society document. The severity of COPD is graded as follows:</p> <p>Mild: FEV_1 50 to 79% of predicted values</p>	<p>Assessment of COPD severity is based on the patients level of symptoms, the severity of the spirometric abnormality, and the presence of complications such as respiratory failure and right heart failure.</p> <p>For educational reasons, a simple classification of disease severity into 4 stages is recommended. The staging is based on airflow limitation as measured by spirometry, which is essential for diagnosis and provides a useful description of the severity of pathological changes in COPD. Specific FEV_1 cut-points (e.g., $< 80\%$ predicted) are used for the purposes of simplicity: these cut-points have not been</p>

	<p>Moderate: FEV₁ 35 to 49% of predicted values Severe: FEV₁ < 35% of predicted values</p> <p>Note: In the presence of obstruction, severity is assessed as a low FEV₁/VC ratio</p>	<p>clinically validated.</p> <p>Stage 0 [At Risk]:</p> <ul style="list-style-type: none"> • Normal spirometry • Chronic symptoms (cough, sputum, production) <p>Stage I [Mild COPD]:</p> <ul style="list-style-type: none"> • FEV₁/FVC <70% • FEV₁ ≥80% predicted • With or without chronic symptoms (cough, sputum production) <p>Stage II [Moderate COPD]:</p> <ul style="list-style-type: none"> • FEV₁/FVC <70% • 30% ≤ FEV₁ <80% predicted <ul style="list-style-type: none"> • (IIA: 50% ≤ FEV₁ <80% predicted) • (IIB: 30% ≤ FEV₁ <50% predicted) • With or without chronic symptoms (cough, sputum production, dyspnea) <p>Stage III [Severe COPD]:</p> <ul style="list-style-type: none"> • FEV₁/FVC <70% • FEV₁ <30% predicted or FEV₁ <50% predicted plus respiratory failure or clinical signs of right heart failure
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Chest X-ray	<p>Chest radiography is diagnostic only of severe emphysema but is essential to exclude other lung diseases.</p>	<p>A chest x-ray is seldom diagnostic in COPD unless obvious bullous disease is present, but it is valuable in excluding alternative diagnoses. Computed tomography (CT) of the chest is not routinely recommended. However, when there is doubt about the diagnosis of COPD, high resolution computed tomography (HRCT) might help in the differential diagnosis. In addition, if a surgical procedure such as bullectomy or lung volume reduction is contemplated, chest computed tomography is most helpful.</p>
Measurement of arterial blood gases/oximetry	<p>Oximetry should be done to help determine if there is a need for oxygen therapy. It may be done at initial assessment or at the time of applying the long-term oxygen therapy.</p> <p>It is unusual that patients with COPD and a PaO_2 of 70 at rest to desaturate low enough to require oxygen. During exercise, noninvasive pulse oximetry may be inaccurate, particularly in patients with poor peripheral perfusion. Verification of oximetry accuracy can be accomplished by obtaining ABG before and after exercise. The level of exercise tested should be appropriate to the patient's normal or anticipated level of activity.</p> <p>In COPD patients who have $\text{PaO}_2 \geq 60$ mmHg during wakefulness, signs of tissue hypoxia occur more often and survival is reduced when sleep desaturation is present (more than five minutes</p>	<p>In advanced COPD, measurement of arterial blood gas is important. This test should be performed in patients with $\text{FEV}_1 < 40\%$ predicted or with clinical signs suggestive of respiratory failure or right heart failure. Clinical signs of respiratory failure include central cyanosis, ankle swelling, and an increase in the jugular venous pressure. Clinical signs of hypercapnia are extremely nonspecific outside of acute exacerbations. Respiratory failure is indicated by a $\text{PaO}_2 < 8.0$ kPa (60 mm Hg) with or without $\text{PaCO}_2 > 6.0$ kPa (45 mm Hg) while breathing air at sea level. Measurement of arterial blood gases should be obtained by arterial puncture; finger or ear oximeters for assessing arterial oxygen saturation (SaO_2) are less reliable.</p>

	<p>during the night). However, studies documenting improved outcome with oxygen supplementation during sleep have yet to be conducted. One night of overnight oximetry is sufficient to determine the presence of arterial oxygen desaturation during sleep. Such desaturation can occur as the patient's COPD evolves with time and the overnight oximetry may need to be repeated at regular intervals (such as six months to yearly) in patients who have or develop an indication.</p>	
<p>Measurement of alpha1-antitrypsin (AAT) levels</p>	<p>AAT deficiency accounts for less than one percent of COPD. If AAT deficiency is suspected, obtain a serum AAT level. Strongly consider referral to specialist in the following situations:</p> <ul style="list-style-type: none"> • Premature onset of COPD with moderate or severe impairment before age 50. • A predominance of basilar emphysema; development of unremitting asthma, especially in a patient under age 50. • A family history of AAT deficiency or of COPD onset before age 50. • Chronic bronchitis with airflow obstruction in a person who has never smoked. • Bronchiectasis, especially in the absence of clear risk factors for the disease. • Cirrhosis in a patient without apparent risk factors. If diagnosis of COPD or asthma is made, refer to specialist 	<p>In patients who develop COPD at a young age (< 45 years) or who have a strong family history of the disease, it may be valuable to identify coexisting AAT deficiency. This could lead to family screening or appropriate counseling. A serum concentration of ATT below 15-20 % of the normal value is highly suggestive of homozygous AAT deficiency.</p>

	for recommendations for therapy.	
Management of Stable COPD Overall Management Strategy		
	VHA/DOD (1999)	WHO/NHLBI (2001)
	Base therapy on symptoms, but consider alternate diagnoses (heart disease, pulmonary emboli, etc.) if out of proportion to spirometry. A stepped-care approach is recommended. Use the lowest level of therapy that satisfactorily relieves symptoms and maximizes activity level. Assure compliance and proper use of medications before escalating therapy.	The overall approach to managing stable COPD should be characterized by a stepwise increase in treatment, depending on the severity of the disease. The management strategy is based on an individualized assessment of disease severity and response to various therapies. Disease severity is determined by the severity of symptoms and airflow limitation, as well as other factors such as the frequency and severity of exacerbations, complications, respiratory failure, comorbidities (cardiovascular disease, sleep related disorders, etc.), and the general health status of the patient. Treatment also depends on the patients educational level and willingness to apply the recommended management, on cultural and local conditions, and on the availability of medications.
Management of Stable COPD Pharmacologic Therapy		
General approach to pharmacologic therapy	<p>The aim of therapy is to use those medications needed to maintain control and improve function and quality of life with the least risk for adverse effects.</p> <p>Typical daily symptoms of COPD include exertional</p>	Pharmacologic therapy is used to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status, and improve exercise tolerance. None of the existing medications for COPD has been shown to

	<p>dyspnea, wheezing, or cough. Chest tightness is common, but should be further evaluated to exclude co-existing heart disease. These symptoms may occur daily or less than daily, thus resulting in different medication recommendations.</p>	<p>modify the long-term decline in lung function that is the hallmark of this disease. However, this should not preclude efforts to use medications to control symptoms.</p>
<p>Short-acting beta-2 agonists (SAIBA)</p>	<ol style="list-style-type: none"> 1. SAIBA are available in MDI, dry powder inhalers, nebulizer and oral forms. They can improve function and quality of life. 2. Short-acting selective inhaled beta₂ agonists such as albuterol are preferred for p.r.n use because of demonstrated efficacy, rapid action, and selective action on airways. The short-acting adrenergic agents have similar efficacy, though inhaled beta₂ selective agents should be favored for lower side effect profiles. 3. SAIBA should be prescribed for p.r.n use in most symptomatic patients with COPD. The usual maximum dose in stable patients is 12 puffs per day for short-acting agents such as albuterol, metaproterenol or terbutaline. Patients who have not responded to greater than maximum doses such as 12 to 20 puffs over three to four hours during an acute exacerbation of COPD should seek medical attention. 4. Symptoms may improve 	<p>Bronchodilator medications are central to the symptomatic management of COPD. They are given either on an as-needed basis for relief of persistent or worsening symptoms, or on a regular basis to prevent or reduce symptoms.</p> <p>Inhaled therapy is preferred. When treatment is given by the inhaled route, attention to effective drug delivery and training in inhaler technique is essential. COPD patients may have more problems in effective coordination and find it harder to use a simple Metered Dose Inhaler (MDI) than do healthy volunteers or younger asthmatics. It is essential to ensure that inhaler technique is correct and to re-check this at each visit.</p> <p>Alternative breath-activated or spacer devices are available for most formulations. Dry powder inhalers may be more convenient and possibly provide improved drug deposition, although this has not been established in COPD. In general, particle deposition will tend to be more central with the fixed airflow limitation and lower inspiratory flow rates in COPD.</p>

	<p>without substantial improvement in FEV₁, indicating that continuation of therapy does not depend on routine assessment with spirometry. For example, SAIBA and ipratropium can improve exercise performance without necessarily improving FEV₁.</p> <p>5. SAIBA, but not ipratropium, may increase the alveolar-arterial oxygen difference, and this may be a reason to decrease the dose of beta₂-agonist while titrating a patients medication.</p>	<p>Wet nebulizers are not recommended for regular treatment because they are more expensive and require appropriate maintenance.</p> <ul style="list-style-type: none"> • Inhaled beta₂-agonists have a relatively rapid onset of bronchodilator effect although this is probably slower in COPD than in asthma. The bronchodilator effects of short-acting beta₂-agonists usually wear off within 4 to 6 hours. • All categories of bronchodilators have been shown to increase exercise capacity in COPD, without necessarily producing significant changes in FEV₁. Regular treatment with short-acting bronchodilators is cheaper but less convenient than treatment with long-acting bronchodilators.
Long-acting beta-agonists	<ol style="list-style-type: none"> 1. The long acting inhaled beta₂-agonist, salmeterol (2 puffs or 50 micrograms bid), is an effective bronchodilator in COPD patients, and has been approved for use in COPD. 2. Salmeterol produces a similar peak bronchodilator response to SAIBA, but the onset is delayed. The bronchodilator effect is prolonged compared to short-acting agents. This has the potential to produce more consistent control of symptoms than SAIBA in some patients. 	<p>Long-acting inhaled bronchodilators are more convenient.</p> <p>Long-acting inhaled beta-agonists, such as salmeterol and formoterol, show a duration of effect of 12 hours or more with no loss of effectiveness overnight or with regular use in COPD patients.</p> <p>In doses of 50 microgram twice daily, but not 100 microgram twice daily, the long-acting inhaled beta₂-agonist salmeterol has been shown to improve health status significantly. Similar</p>

	<ol style="list-style-type: none"> 3. Chronic use is not associated with significant tachyphylaxis, and may decrease the need for rescue use of SAIBA. 4. Strong evidence for symptomatic benefit of salmeterol over other regularly inhaled short acting bronchodilators in patients with COPD is not currently available. Thus, its place in the scheme of therapy is not well defined at this time. It may be considered for patients whose need for SAIBA exceeds 8 to 12 puffs daily. 5. The principle advantage of salmeterol is its long duration of action, which may be of benefit in treating nocturnal dyspnea. Additionally, enhanced compliance with a twice daily rather than q.i.d regimen may provide smoother symptomatic control. 6. Because the onset and duration of action are both prolonged compared to SAIBA, salmeterol should not be used for p.r.n, rescue use. Patients should be educated to continue to use SAIBA p.r.n. 7. Oral forms of beta₂-agonists may be useful in patients who cannot use any inhaled form, although such cases are rare. The risk of systemic adverse reactions is increased significantly with oral beta₂-adrenergic bronchodilators. 8. Inhaled salmeterol should be continued 	<p>data for short-acting beta₂-agonists are not available.</p>
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	only in those patients who experience symptomatic benefit from its addition to their regimen.	
Inhaled anticholinergics	<ol style="list-style-type: none"> 1. Ipratropium bromide, the prototype anticholinergic bronchodilator, is available as a metered dose inhaler (MDI) or as a nebulizer solution. 2. Ipratropium bromide has similar, or according to some studies, greater efficacy than SAIBA. It has a slower onset of action, a longer duration of action, and minimal systemic absorption. It may cause fewer systemic side effects than beta₂-agonists. For these reasons, it is preferred as a regularly scheduled inhaled bronchodilator. 3. In patients with COPD, ipratropium bromide at peak effect typically increases the FEV₁ by 0.15 to 0.35 L. At high doses, ipratropium bromide can improve exercise tolerance. 4. The starting dose of ipratropium should be at least two puffs t.i.d. Use of typical recommended doses of ipratropium (two puffs q.i.d) produces less than maximal bronchodilation. Improvement in pulmonary function is maximal at 6 to 14 puffs as a single dose of ipratropium. If symptoms do not resolve with two to four puffs q.i.d, up to six and 	<p>Use of inhaled ipratropium (an anticholinergic) four times daily improves health status.</p> <p>The bronchodilating effect of short-acting inhaled anticholinergics lasts longer than that of short-acting beta₂-agonists, with some bronchodilator effect generally apparent up to 8 hours after administration.</p>

	<p>possibly eight puffs q.i.d may be needed. Improvement in level of function and in activities in daily living can be used to guide therapy. The risk of toxicity at higher doses appears to be relatively low compared to inhaled beta₂-agonists.</p> <p>5. The sequence of administration of ipratropium and SAIBA does not generally make any difference in the bronchodilator benefit.</p>	
<p>Combination therapy with inhaled anticholinergics and short-acting beta₂ agonists</p>	<p>1. Patients with COPD whose symptoms are inadequately controlled with the recommended doses of either an inhaled short acting inhaled beta₂-agonist or ipratropium should be treated with a combination of both inhaled agents. The combination at recommended doses provides added symptomatic benefit without incurring the risk of toxicity from using very high doses of single agents.</p> <p>2. SAIBA may be added to ipratropium as regularly scheduled medications, typically two to four puffs q.i.d, as well as additional p.r.n dosing, to a usual recommended maximum of 12 puffs per day. Demonstration of an acute improvement in FEV₁ is not necessary in order to obtain clinical benefit. The lack of an</p>	<p>Combining drugs with different mechanisms and durations of action may increase the degree of bronchodilation for equivalent or lesser side effects. A combination of a short-acting beta₂-agonist and the anticholinergic drug ipratropium in stable COPD produces greater and more sustained improvements in FEV₁ than either drug alone and does not produce evidence of tachyphylaxis over 90 days of treatment. The combination of a beta₂-agonist, an anticholinergic, and/or theophylline may produce additional improvements in lung function and health status. Increasing the number of drugs usually increases costs, and an equivalent benefit may occur by increasing the dose of one bronchodilator when side effects are not a limiting factor. Detailed assessments of this approach have not been carried out.</p>

	<p>immediate bronchodilator response should not preclude a clinical trial of these medications.</p> <ol style="list-style-type: none"> 3. As the dose of ipratropium or inhaled SAIBA increases, the added benefit becomes less from the other agent, but some patients will have an added benefit even with high doses of each. There is no way to predict, other than in a trial of therapy, which patients will have this combined effect. 4. A product that dispenses 90 micrograms albuterol and 18 micrograms ipratropium per puff from one metered dose inhaler is available commercially (Combivent™). This should not generally be used as a first line agent, but may provide enhanced compliance and resultant benefit in patients who require combination therapy. Patients taking a regularly scheduled combination inhaler should continue to use a SAIBA for breakthrough symptoms. 	
Methylxanthines	<ol style="list-style-type: none"> 1. Theophylline can be added to improve pulmonary function, symptoms, or activities in patients with COPD who do not achieve adequate symptom control with inhaled bronchodilators. 2. Many theophylline preparations are 	<p>Theophylline is effective in COPD, but due to its potential toxicity inhaled bronchodilators are preferred when available. All studies that have shown efficacy of theophylline in COPD were done with slow-release preparations.</p>

	<p>available, but sustained release formulations may provide longer control and better benefit for nocturnal dyspnea.</p> <ol style="list-style-type: none"> 3. Theophylline has a narrow therapeutic index, with the potential for dose related adverse reactions that include insomnia, anxiety, nausea, vomiting, tremor, arrhythmias, delirium, seizures, and death. 4. Typical starting doses are 400 to 600 mg daily, but blood levels should be measured carefully at the start of therapy. The therapeutic target for most patients should be a blood level of 10 micrograms/ml (range 5-12 micrograms/ml). In some cases, if benefit has been demonstrated and with careful monitoring, a blood level of 15 micrograms/ml of theophylline can be a therapeutic target. However, with an increase in concentrations over 12 micrograms/ml, the risk to benefit ratio increases, especially in older patients. After initial stability, repeat levels should be obtained when symptoms change, acute illness develops, potentially interacting drugs are added, non-compliance is suspected, dose adjustments are made, or symptoms suggestive of toxicity develop. 5. Drug interactions with theophylline are 	
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	<p>common, and may either increase or decrease theophylline metabolism. All changes in medical regimens should be evaluated for potential impact on theophylline levels.</p> <p>6. Theophylline should be continued only in patients who demonstrate a symptomatic benefit, such as improved dyspnea or exercise tolerance. The improvement in function from theophylline may not be evident in pulmonary function testing. However, therapy should be discontinued in patients who demonstrate no subjective or objective improvement after several weeks of theophylline therapy.</p>	
Corticosteroids	<ol style="list-style-type: none"> 1. Unlike the high response rate seen in asthma, in patients with COPD a response to chronic oral corticosteroid use is beneficial in less than about 20 to 25 percent. The benefit from inhaled steroids is not precisely defined. 2. Patients on maximal bronchodilator therapy who have not had a satisfactory response may be considered candidates for a corticosteroid trial. An objective measure of improvement should be sought in all patients undergoing a steroid trial. A response may be defined as an 	<p>Prolonged treatment with inhaled glucocorticosteroids does not modify the long-term decline in FEV₁ in patients with COPD. Regular treatment with inhaled glucocorticosteroids or in those with an FEV₁ <50% predicted (Stage IIB: Moderate COPD and Stage III: Severe COPD) is only appropriate for symptomatic COPD patients with a documented spirometric response to inhaled glucocorticosteroids and repeated exacerbations requiring treatment with antibiotics or oral glucocorticosteroids. The dose-response relationship and long-term safety of inhaled glucocorticosteroids</p>

	<p>improvement in symptoms and an increase in FEV₁ of ≥ 20 percent from baseline. An objective measurement of the steroid effects can only be obtained in patients who are otherwise stable.</p> <ol style="list-style-type: none"> 3. A typical trial of oral prednisone is 40 to 60 mg/day for 10 to 14 days. There is less published experience with high-dose inhaled steroids, but in some patients this may be a reasonable alternative. The appropriate dose of inhaled steroids has not been determined, but a trial for 14 to 21 days of the equivalent of beclomethasone 1500 micrograms/day (30 puffs) or fluticasone 880 micrograms /day has been suggested. 4. Patients who show no objective response to a steroid trial should have their steroids promptly discontinued. Patients who have a response should be tapered to the lowest possible dose. Supplementation or substitution with a high-dose inhaled steroid may allow further reduction or discontinuation of the oral steroid. 5. Adverse effects of oral corticosteroids are numerous and include: hypertension, hyperglycemia, weight gain, immunosuppression, skin thinning, personality changes, purpura, mental status 	<p>in COPD are not known.</p> <p>The present guidelines recommend a trial of 6 weeks to 3 months with inhaled glucocorticosteroids to identify COPD patients who may benefit from long-term inhaled glucocorticosteroid therapy. Many existing COPD guidelines recommend the use of a short course (two weeks) of oral glucocorticosteroids to identify COPD patients who might benefit from long-term treatment with oral or inhaled glucocorticosteroids. There is mounting evidence, however, that a short course of oral glucocorticosteroids is a poor predictor of the long-term response to inhaled glucocorticosteroids in COPD. Long-term treatment with oral glucocorticosteroids is not recommended in COPD. There is no evidence of long-term benefit from this treatment. Moreover, a side effect of long-term treatment with systemic glucocorticosteroids is steroid myopathy, which contributes to muscle weakness, decreased functionality, and respiratory failure in patients with advanced COPD.</p>
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	<p>changes, depression, glaucoma, cataracts, and adrenal suppression. Patients requiring long-term steroids should be evaluated for risk of osteoporosis and preventive measures instituted, such as calcium and vitamin D supplements, weight-bearing exercise and hormone replacement therapy if appropriate. The risks of long-term treatment should be discussed with the patient.</p> <p>6. The role of chronic inhaled corticosteroids in COPD remains under investigation. Preliminary work suggests that chronic inhaled steroid use may slow the rapid decline in FEV₁ typically seen in patients with COPD. Response to an oral steroid trial, as well as a brisk bronchodilator response may help identify patients who will respond better to inhaled steroids.</p> <p>7. The use of MDI spacers and rinsing of the mouth after drug use is recommended to help improve drug delivery to the lung and avoid local complications, such as hoarseness or oral candidiasis.</p>	
<p align="center">Management of Stable COPD Non-pharmacologic Treatment</p>		
	VHA/DOD (1999)	WHO/NHLBI (2001)
Long-term	Patient should be on	LTOT is generally introduced

<p>oxygen therapy (LTOT)</p>	<p>maximal medical therapy and stable for 30 days before decisions about LTOT are made. Short-term oxygen may be instituted in the interim. In addition to treating acute exacerbations, therapy to correct anemia and congestive heart failure should be instituted. Intensify smoking cessation efforts, since smoking poses a safety hazard for patients on LTOT. The benefits of long-term oxygen therapy may not be realized in patients who continue to smoke and have high levels of carboxyhemoglobin.</p> <p>The precise PaO₂ level to improve quality of life or increase survival has not been well defined. Arterial oxygen saturations of 90 to 92 percent or PaO₂ of 60 to 65 mmHg are usual acceptable targets because of the shape of the oxygen hemoglobin saturation curve. Ambulatory patients should be provided ambulatory and stationary oxygen equipment to reach the target of use 24 hours a day to correct PaO₂ greater or equal 60 or SaO₂ greater or equal 90 percent. Immobile patients may only require a stationary system with a portable system for use during transport. In most cases, changes in flow rate are not indicated for sleep and exercise. Some authorities recommend increasing flow rates by one liter per minute to treat possible desaturation during sleep, but evidence for this approach is not strong. If there are signs of cor pulmonale despite adequate daytime oxygenation, the patient may be monitored</p>	<p>in <i>Stage III: Severe Chronic Obstructive Pulmonary Disease</i> for patients who have:</p> <ul style="list-style-type: none"> • PaO₂ at or below 7.3 kPa (55 mm Hg) or SaO₂ at or below 88%, with or without hypercapnia; or • PaO₂ between 7.3 kPa (55 mm Hg) and 8.0 kPa (60 mm Hg) or SaO₂ 89%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive heart failure, or polycythemia (hematocrit >55%). <p>The goal of LTOT is to increase the baseline PaO₂ to at least 8.0 kPa (60 mm Hg) at sea level and rest, and/or produce SaO₂ at least 90%, which will preserve vital organ function by ensuring an adequate delivery of oxygen.</p> <p>A decision about the use of LTOT should be based on the waking PaO₂ values. The prescription should always include the source of supplemental oxygen (gas or liquid), the method of delivery, duration of use, and the flow rate at rest, during exercise, and during sleep.</p>
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	<p>with oximetry during sleep to determine the best sleep setting. Some patients may be candidates for oxygen-conserving devices (e.g., reservoir cannulae, demand oxygen delivery device, transtracheal oxygen) to improve mobility and portability of oxygen therapy.</p>	
<p style="text-align: center;">Management of Stable COPD Preventive Care and Patient Education</p>		
<p>Smoking Cessation</p>	<p>All smokers should be strongly advised to quit. Smoking cessation results in a small improvement in lung function and a slowing of the rate of decline to approximately that seen in never smokers of the same age. Patients not willing to quit should receive motivational intervention to promote subsequent quitting attempts. The smoker willing to make a quit attempt should be assisted by being asked to set a quit date, providing self-help materials, encouraging nicotine replacement therapy, and referring to intensive treatments when appropriate. All patients attempting to quit should have follow-up contact scheduled.</p>	<p>Comprehensive tobacco control policies and programs with clear, consistent, and repeated non-smoking messages should be delivered through every feasible channel. Legislation to establish smoke-free schools, public facilities, and work environments should be encouraged by government officials, public health workers, and the public.</p> <p>Smoking cessation is the single most effective — and cost-effective — way to reduce the risk of developing COPD and stop its progression. Even a brief, three-minute period of counseling to urge a smoker to quit can be effective, and at the very least this should be done for every smoker at every visit. Health education, public policy, and information dissemination programs are all vital components in a comprehensive cessation effort.</p> <p><i>Guidelines for Smoking Cessation:</i> Guidelines for smoking cessation were published by the United States Agency for Health Care Policy and Research (AHCPR) (now the Agency</p>

		<p>for Healthcare Research and Quality [AHRQ] in 1996 and updated in 2000 by the United States Public Health Service in the publication titled "Treating Tobacco Use and Dependence: A Clinical Practice Guideline" (see the related National Guideline Clearinghouse Guideline Summary).</p> <p>Smoking Cessation Intervention Process: The Public Health Service Report recommends a five-step program for intervention, which provides a strategic framework helpful to health care providers interested in helping their patients stop smoking. Three types of counseling are especially effective: (1) practical counseling, (2) social support as part of treatment, and (3) social support arranged outside of treatment.</p> <p><i>Pharmacotherapy:</i> Numerous effective pharmacotherapies for smoking cessation now exist. Except in the presence of special circumstances, pharmacotherapy is recommended when counseling is not sufficient to help patients quit smoking. Special consideration should be given before using pharmacotherapy in selected populations: people with medical contraindications, light smokers fewer than 10 cigarettes/day, and pregnant and adolescent smokers.</p>
Vaccines	The Advisory Committee on Immunization Practices (U.S. Centers for Disease Control and Prevention) recommends pneumococcal vaccination for all patients	Influenza vaccines can reduce serious illness and death in COPD patients by about 50%. Vaccines containing killed or live, inactivated viruses are

	<p>with COPD. They recommend that patients age 65 or older that were vaccinated more than five years previously should be revaccinated. When the status of previous vaccination is unsure, vaccination is indicated. However, the evidence for the efficacy of <i>pneumococcal vaccination</i> in patients with COPD is inconclusive. One small, randomized controlled trial failed to demonstrate vaccine efficacy for pneumococcal infection-related or other medical outcomes in the heterogeneous group of subjects labeled as high-risk. Case-controlled trials suggest an effectiveness of 65 to 84 percent among high-risk patients including those with COPD.</p> <p>An annual <i>influenza vaccination</i> is recommended for individuals with chronic pulmonary disease unless contraindicated due to severe anaphylactic hypersensitivity to egg protein. Influenza vaccination has been shown to be 30 to 80 percent effective in preventing illness, complications, and death in high-risk populations. Pneumococcal and influenza vaccines can be administered concurrently at different sites without increasing side effects.</p>	<p>recommended, and should be given once (in Autumn) or twice (in Autumn and Winter) each year. A pneumococcal vaccine containing 23 virulent serotypes has been used but sufficient data to support its general use in COPD patients are lacking.</p>
Management of environment	<p>Patients with COPD should avoid environmental exposures that exacerbate their symptoms (e.g., occupational exposures, second-hand smoke, and air and dust pollution) or results in respiratory infections.</p>	<p>Reduction of total personal exposure to tobacco smoke, occupational dusts, and chemicals, and indoor and outdoor air pollutants are important goals to prevent the onset and progression of chronic obstructive</p>

		pulmonary disease.
Patient education	<p>The main items in COPD patient education are:</p> <ul style="list-style-type: none"> • Smoking Cessation • Medication and delivery system training • Exercise and nutritional counseling • Need for immunizations • Management of environment • Self-assessment and self-management • Occupational disabilities • Sexual function 	<p>Although patient education alone does not improve exercise performance or lung function, it can play a role in improving skills, ability to cope with illness, and health status. In addition, patient education is effective in accomplishing certain specific goals, including smoking cessation, initiating discussions and understanding of advanced directives and end-of-life issues, and improving patient responses to acute exacerbations.</p> <p>Education may take place in many settings: consultations with physicians or other health care workers, home care or outreach programs, and comprehensive pulmonary rehabilitation programs. It should be tailored to the needs and environment of the patient, interactive, directed at improving quality of life, simple to follow, practical, and appropriate to the intellectual and social skills of the patient and the caregiver. The topics that seem most appropriate for an education program to cover include: smoking cessation; basic information about chronic obstructive pulmonary disease and pathophysiology of the disease; general approach to therapy and specific aspects of medical treatment; self-management skills; strategies to help minimize dyspnea; advice about when to seek help; self-management and decision-making in exacerbations; and advance directives and end-</p>

		of-life issues.
Ongoing Assessment and Follow-up		
	<p>For mild COPD, spirometry is the test used for measuring disease progression. As the disease becomes more severe, oximetry and arterial blood gas analysis assume greater importance. The frequency of obtaining these measures is based on clinical symptoms and status. In general, patients with mild COPD should be seen annually; moderate COPD, six months to one year, depending upon status; and severe COPD, every six months at a minimum. Spirometry should be repeated at least every two to three years to follow the progression of disease and effects of therapy unless there is a clinically indicated reason not to do so.</p>	<p><i>Monitoring Disease Progression and Development of Complications:</i> COPD is usually a progressive disease, and a patients lung function can be expected to worsen over time, even with the best available care. Symptoms and objective measures of airflow limitation should be monitored for development of complications and to determine when to adjust therapy.</p> <p>Follow-up visits should include a discussion of new or worsening symptoms. Spirometry should be performed if there is a substantial increase in symptoms or a complication. Measurement of arterial blood gas tensions should be considered in all patients with an FEV₁ <40% predicted or clinical signs of respiratory failure or right heart failure. Elevation of the jugular venous pressure and the presence of pitting ankle edema are often the most useful findings suggestive of right heart failure in clinical practice. Measurement of pulmonary arterial pressure is not recommended in clinical practice as it does not add practical information beyond that obtained from a knowledge of PaO₂.</p> <p><i>Monitor Pharmacotherapy and Other Medical Treatment:</i> In order to adjust therapy appropriately as the disease progresses, each follow-up visit should include</p>

		<p>a discussion of the current therapeutic regimen. Dosages of various medications, adherence to the regimen, inhaler technique, effectiveness of the current regime at controlling symptoms, and side effects of treatment should be monitored.</p> <p><i>Monitor Exacerbation History:</i> Frequency, severity, and likely causes of exacerbations should be evaluated. Increased sputum volume, acutely worsening dyspnea, and the presence of purulent sputum should be noted. Severity can be estimated by the increased need for bronchodilator medication or glucocorticosteroids and by the need for antibiotic treatment. Hospitalizations should be documented, including the facility, duration of stay, and any use of critical care or intubation.</p> <p><i>Monitor Comorbidities:</i> In treating patients with chronic obstructive pulmonary disease, it is important to consider the presence of concomitant conditions such as bronchial carcinoma, tuberculosis, sleep apnea, and left heart failure. The appropriate diagnostic tools (chest x-ray, electrocardiogram, etc.) should be used whenever symptoms (e.g., hemoptysis) suggest one of these conditions.</p>
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TABLE 3: BENEFITS AND HARMS

VHA/DOD (1999)	WHO/NHLBI (2001)
BENEFITS	
<p><i>Overall Benefits of Guideline Recommendations</i> The ultimate goal of this guideline is to promote evidence-based management of persons with COPD and thereby improve clinical outcomes.</p> <p>This guideline can assist primary care providers of specialists in the early detection of symptoms, assessment of the clinical situation, determination of appropriate treatment, and delivery of individualized interventions.</p> <p>Appropriate use of medications for asthma or chronic obstructive pulmonary disease may alleviate symptoms, increase exercise tolerance, improve pulmonary function, and improve quality of life.</p> <p><i>Long-term oxygen therapy</i> In COPD patients with hypoxemia and cor pulmonale, long-term oxygen therapy (LTOT) may increase the life span by 6 to 7 years. Mortality is reduced in patients with chronic hypoxemia when oxygen is administered for more than 12 hours daily and greater survival benefits have been shown with continuous oxygen administration.</p> <p><i>Pneumococcal vaccination</i> Most studies show a benefit, but one small randomized, placebo-controlled trial did not. Case-controlled trials suggest an effectiveness (prevention of pneumococcal infection) of 65 to 84 percent among high-risk patients including those with COPD.</p> <p><i>Annual influenza vaccination</i> Influenza vaccination has been shown to be 30 to 80 percent effective in preventing illness, complications, and death in high-risk populations (such as</p>	<p><i>Overall Benefits of Guideline Recommendations</i></p> <ul style="list-style-type: none"> • The goals of effective COPD management are to: <ul style="list-style-type: none"> • Prevent disease progression • Relieve symptoms • Improve exercise tolerance • Improve health status • Prevent and treat complications • Prevent and treat exacerbations • Reduce mortality • COPD prevention <p><i>Long term oxygen therapy</i> The long-term administration of oxygen (> 15 hours per day) to patients with chronic respiratory failure has been shown to increase survival. It can also have a beneficial impact on hemodynamics, hematologic characteristics, exercise capacity, lung mechanics, and mental state.</p> <p><i>Smoking cessation</i> Patient education regarding smoking cessation has the greatest capacity to influence the natural history of COPD. Evaluation of the smoking cessation component in a long-term, multicenter study indicates that if effective resources and time are dedicated to smoking cessation, 25% long-term quit rates can be maintained.</p>

<p>COPD).</p> <p><i>Smoking cessation</i> Smoking cessation results in a small improvement in lung function and a slowing of the rate of decline to approximately that seen in never smokers of the same age.</p>	
<p>HARMS</p>	
<p><i>Short-acting inhaled beta₂-agonists (SAIBA)</i> Inhaled beta₂-agonists may cause tremor, increased heart rate, insomnia, restlessness, hypokalemia, or a paradoxical reduction in arterial oxygenation.</p> <p><i>Inhaled anticholinergic agent (i.e., ipratropium)</i> Inhaled ipratropium may cause dry mouth or increased heart rate, or exacerbate glaucoma, benign prostatic hypertrophy or other conditions potentially worsened by the drugs anticholinergic activity.</p> <p><i>Steroids, oral and inhaled</i> Adverse effects of oral corticosteroids are numerous and include: hypertension, hyperglycemia, weight gain, immunosuppression, skin thinning, personality changes, purpura, mental status changes, depression, glaucoma, cataracts, and adrenal suppression. Patients requiring long-term steroids should be evaluated for risk of osteoporosis and preventive measures instituted, such as calcium and vitamin D supplements, weight-bearing exercise and hormone replacement therapy if appropriate.</p> <p>Adverse effects of inhaled corticosteroids include oral candidiasis, hoarseness, and possible adrenal suppression at high doses.</p> <p><i>Theophylline</i> Theophylline has a narrow therapeutic index, with the potential for dose related adverse reactions that include</p>	<p><i>Beta₂-agonists:</i> Stimulation of beta₂-receptors can produce resting sinus tachycardia and has the potential to precipitate cardiac rhythm disturbances in very susceptible patients, although this appears to be a remarkably rare event with inhaled therapy. Exaggerated somatic tremor is troublesome in some older patients treated with higher doses of beta₂-agonists, whatever the route of administration, and this limits the dose that can be tolerated.</p> <p>Although hypokalemia can occur, especially when treatment is combined with thiazide diuretics, and oxygen consumption can be increased under resting conditions, these metabolic effects show tachyphylaxis unlike the bronchodilator actions. Mild falls in PaO₂ occur after administration of both short- and long-acting beta₂-agonists, but the clinical significance of these changes is doubtful. Despite the concerns raised some years ago, further detailed study has found no association between beta₂-agonist use and an accelerated loss of lung function or increased mortality in chronic obstructive pulmonary disease.</p> <p><i>Anticholinergics:</i> Anticholinergic drugs, such as ipratropium bromide, are poorly absorbed, which limits the troublesome systemic effects seen with atropine. Extensive use of this class of inhaled agents in a wide range of doses and clinical settings has shown them to be very safe. Although occasional prostatic symptoms have been reported, there are no data to prove a true causal</p>

<p>insomnia, anxiety, nausea, vomiting, tremor, arrhythmias, delirium, seizures, and death.</p> <p>Drug interactions with theophylline are common, and all changes in a patients medical regimen should be reviewed for their potential impact on serum theophylline levels.</p> <p>Attempts to withdraw theophylline, even at lower levels, should be done cautiously, since deterioration in pulmonary function and exercise performance may occur.</p>	<p>relationship. A bitter, metallic taste is reported by some patients using ipratropium.</p> <p><i>Methylxanthines:</i> Toxicity is dose related, a particular problem with the xanthine derivatives because their therapeutic ratio is small and most of the benefit occurs only when near-toxic doses are given. Methylxanthines are nonspecific inhibitors of all phosphodiesterase enzyme subsets, which explains their wide range of toxic effects. Problems include the development of atrial and ventricular arrhythmias (which can prove fatal) and grand mal convulsions (which can occur irrespective of prior epileptic history). More common and less dramatic side effects include headaches, insomnia, nausea, and heartburn, and these may occur within the therapeutic range of serum theophylline. Unlike the other bronchodilator classes, xanthine derivatives may involve a risk of overdose (either intentional or accidental).</p> <p><i>Oral Glucocorticosteroids:</i> A side effect of long-term treatment with systemic glucocorticosteroids is steroid myopathy, which contributes to muscle weakness, decreased functionality, and respiratory failure in subjects with advanced chronic obstructive pulmonary disease.</p>
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GUIDELINE CONTENT COMPARISON

Veterans Health Administration/Department of Veterans Affairs (VHA/DOD) and World Health Organization/National Heart, Lung, and Blood Institute (WHO/NHLBI) present recommendations for the diagnosis and management of stable chronic obstructive pulmonary disease (COPD) and provide explicit reasoning behind their judgments. Both VHA/DOD and WHO/NHLBI identify the type of supporting evidence for selected recommendations. The reader is directed to the original guidelines for the evidence grades for specific recommendations.

As mentioned in the introduction above, there are some differences in the scope and format of the guidelines. The VHA/DOD guideline (with

accompanying clinical algorithms) is expressed in 10 modules, divided into two major sections: outpatient management and inpatient (emergency room and hospital ward) interventions. The guideline addresses diagnosis, assessment, pharmacotherapy, and non-pharmacologic therapy (e.g. oxygen therapy) in patients with chronic, stable disease and in patients with acute exacerbation of COPD. The VHA/DOD guideline also provides recommendations for management of air travel and insomnia in COPD and for preoperative evaluation and management.

The WHO/NHLBI guideline differs from the VHA/DOD guideline in its global perspective and in its emphasis on prevention strategies. This guideline presents a COPD management plan with four components: (1) assessment and monitoring of disease, (2) reduction of risk factors, (3) management of stable COPD, and (4) management of exacerbations. The WHO/NHLBI guideline also differs from the VHA/DOD guideline in including recommendations for pulmonary rehabilitation and surgical treatment of COPD.

Areas of Agreement

Definitions/signs and symptoms of COPD

The guidelines are in general agreement concerning the definition of COPD. Both groups agree that airflow obstruction that is not fully reversible is necessary for the diagnosis.

Medical history

VHA/DOD and WHO/NHLBI provide recommendations on items to include in the medical history of a patient with suspected or confirmed COPD. Specific assessments to be made vary slightly between the guidelines; however, both agree that medical history should include questions about symptoms, risk factors (especially environmental factors), comorbid conditions, and current therapy.

Physical Examination

VHA/DOD and WHO/NHLBI include recommendations for physical examination of the patient with suspected or confirmed COPD, with emphasis on chest examination. Again, there are some differences in the items for inclusion in the examination, but common elements are respiratory rate, presence of cyanosis, accessory muscle use, presence of edema, signs of airflow obstruction, chest wall abnormalities, breath and heart sounds, signs of pursed-lip breathing and wheezing.

Measurement of airflow limitation — spirometry

Both VHA/DOD and WHO/NHLBI agree that spirometry pre- and postbronchodilation are essential to confirm the presence and reversibility of airflow obstruction in patients with suspected or confirmed stable COPD.

Chest X-Ray

VHA/DOD and WHO/NHLBI acknowledge that chest X-ray is seldom diagnostic in patients with suspected or confirmed COPD but that chest radiography is essential to excluding alternative lung diseases.

Measurement of arterial blood gases

VHA/DOD and WHO/NHLBI agree that measurement of arterial blood gases

is valuable in patients with suspected or confirmed stable COPD to evaluate the need for oxygen therapy.

Measurement of alpha1-antitrypsin (AAT) levels

Both VHA/DOD and WHO/NHLBI are in agreement that AAT deficiency should be suspected and AAT levels measured in patients who develop COPD at a relatively young age or who have a strong family history of COPD or AAT deficiency. VHA/DOD specifies age < 50 years and WHO/NHLBI specifies age < 45 years as the cut-off age for premature onset of symptoms. VHA/DOD lists some additional clinical features that may be cause for specialist referral for AAT deficiency that are not mentioned by WHO/NHLBI (see [Table 2](#) above).

Overall management strategy and general approach to pharmacologic therapy

The guidelines are in general agreement that a stepped approach to treatment should be used, with therapy based on severity of symptoms and coexisting conditions.

Bronchodilators

VHA/DOD and WHO/NHLBI present similar recommendations on the use and efficacy of the various types of bronchodilating drugs. Short-acting or long-acting beta₂-agonists and inhaled anticholinergics, alone or in combination, are recommended for symptom control.

Corticosteroids

VHA/DOD and WHO/NHLBI are in general agreement that inhaled steroids should not be used routinely in patients with stable COPD, and that long-term steroid use is still controversial. Both guidelines recommend a short-term trial of oral steroids to ascertain responsiveness, although WHO/NHLBI maintains there is mounting evidence that short-term oral steroid is a poor predictor of long-term response to inhaled steroids.

Long-term oxygen therapy

Both guidelines recognize the benefits of long-term oxygen therapy in patients with severe COPD. Arterial oxygen saturation of 90-92% or PaO₂ of at least 60 mm Hg should be targeted.

Smoking Cessation

VHA/DOD and WHO/NHLBI agree that all smokers should be encouraged to quit and be given motivational and instructional support to do so. Nicotine replacement therapy should be provided when appropriate.

Immunizations

Both VHA/DOD and WHO/NHLBI recommend annual influenza vaccines in patients with COPD to reduce the risk of death and serious complications. Both guidelines state that although pneumococcal vaccines are used in this population, evidence for its efficacy is lacking.

Management of environment

The guidelines are in agreement that patients with COPD should be advised to avoid environmental triggers of COPD symptoms, such as air pollution, dust, and second-hand smoke.

Patient education

VHA/DOD and WHO/NHLBI both acknowledge the benefits of patient education. Some of the items that constitute a comprehensive course mentioned by both guidelines are smoking cessation counseling, self-assessment, and self-management.

Ongoing assessment and follow-up

The guidelines are in agreement that follow-up is necessary in COPD, since the disease is usually progressive. Spirometry and blood gas analysis are two objective measures of airflow limitation that should be employed based on severity of symptoms. VHA/DOD recommends spirometry every 2 to 3 years, whereas WHO/NHLBI suggests that spirometry should be performed only if there is an increase in symptoms or complications.

Areas of Differences

Assessing severity of disease

Recommendations between the groups differ somewhat regarding assessment of disease severity. VHA/DOD recommends use of the American Thoracic Society system for staging, whereas WHO/NHLBI recommends use of a four-stage system. WHO/NHLBI points out that this staging system "should only be regarded as an educational tool, and a very general indication of the approach to management." It was not clinically validated. Both VHA/DOD and WHO/NHLBI agree that severity of COPD can be graded as mild, moderate, or severe based on airflow limitation as measured by spirometry. WHO/NHLBI also lists a Stage 0 disease, in which a person has chronic symptoms of COPD but normal spirometry. In addition, WHO/NHLBI subdivides moderate disease into stage IIA and IIB. Both groups define moderate to severe COPD as an $FEV_1 \leq 50$ percent of predicted, although WHO/NHLBI defines severe as an $FEV_1 \leq 30$ percent and VHA/DOD defines severe as $FEV_1 \leq 35$ percent of predicted.

Methylxanthines

VHA/DOD notes that theophylline can be added to improve pulmonary function, symptoms, or activities in patients with COPD who do not achieve adequate symptom control with inhaled bronchodilators. WHO/NHLBI notes that theophylline is effective in COPD, but due to its potential toxicity inhaled bronchodilators are preferred when available. Both guidelines recognize the potential for significant toxicity from theophylline, and therefore, it is not recommended as first-line therapy. When used, slow-release preparations are preferable.

Updates in Progress: The organizations represented in this Synthesis are not in the process of updating their guidelines.

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